Letter from the Director

by Charlie Strange, M.D.
Professor of Pulmonary and Critical Care Medicine, Allergy and Clinical Immunology
Medical University of South Carolina

Dear Registry Members,

This 2005 spring edition of the Registry newsletter brings all of us closer to fulfilling the mission of the Alpha-1 Foundation. For those who haven’t memorized the mission statement it is to provide the leadership and resources that will result in increased research, improved health, worldwide detection and a cure for Alpha-1. While we have not yet found the cure for Alpha-1, you will see from the articles in this issue that science continues to whittle away at the unknowns in Alpha-1 Antitrypsin Deficiency.

You will find some strong messages about body weight and alcohol use in the Registry study on liver disease. We are all extremely proud of the Alphas who participated in this questionnaire study describing 84% of the liver affected Alphas in the Registry. We thank Dr. Chris Bowlus at the University of California at Davis for initiating this study nearly two years ago.

Some surprises about the frequency of allergy symptoms and asthma have come from Dr. Ed Eden’s study that is summarized in this issue of the newsletter. As you may remember, this was a study in which the PiMZ carriers could participate. In all, 757 questionnaires were received and collated at the Registry for this study making this the largest study on asthma ever conducted in Alpha-1.

There have been some disappointments as well. New drug studies for Alpha-1 have not begun at the rate that many of us were hoping. Therefore, we are happy to report that an invitation for a new augmentation therapy study will be coming to you soon. This is a welcome addition for a community that is used to advancing the science of their disease.

The Registry continues to grow and the April 1, 2005 figure now stands at 2808 individuals. We hope to surpass the 3000 Alphas milestone by the end of the year. Please spread the word among your Alpha-1 friends and family members to help us reach our goal. If a copy of the Registry newsletter does not come by mail to your door, please call us toll free to update your mailing information and assure that you are a member. Remember that the Registry accepts PiZZ, PiSZ, PiMZ and rare phenotypes making many family members eligible even in the absence of symptoms.

Lastly, there is a large national push to assure that physician testing for Alpha-1 includes all COPD patients and those whose asthma does not completely respond to therapy. It regular testing is not the practice of your physician, then every voice of education is helpful. Who is better to educate your physician than you? Ask the question and listen carefully to the answer. Thank you for being a member of the Alpha-1 Research Registry.

Sincerely,

Charlie Strange, M.D.
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Are You Getting This Newsletter in a Brown Paper Wrapper?
by Yonge R. Jones, Alpha-1 Research Registry Coordinator

Twice yearly the staff of the Alpha-1 Research Registry, in cooperation with the Alpha-1 Foundation, produces an informative newsletter for the many Alphas located in America and abroad. We try to make the Registry newsletter full of interesting articles including medical and investigational information devoted to the many members of the Research Registry. Our appeal to the many physicians and researchers for articles has always been and continues to be met with a resounding “yes” by article authors. Their continued involvement makes our job at the Registry easy.

The publication process culminates on the magical day when many boxes arrive from our printer and the real work begins – The stuffing of the newsletters into brown envelopes for mailing. Since the newsletter also serves as a marketing tool to help others join the Registry and keep the Researchers up to date on the field, we worry that everyone gets the Newsletter and thinks they are in the Registry when they might not be.

We would like to know - “are you getting the newsletter in a brown paper wrapper?” Our mailings are designed to send the newsletters to each of you in the most unobtrusive manner. The plain envelope, we found, is the best way to send the publication anonymously. Are we reaching you? If yours doesn’t come this way, give us a call to assure that you are in the Registry. In closing, my first year at the Registry has been wonderful! Thank you for all of your kind words of support and my privilege to speak to the many Alphas out there.
Alpha-1 Research Registry

Genetic Testing in Children and Adolescents
by M. Allison Mosley
Alpha-1 Research Registry
Medical University of South Carolina

Alpha-1 Antitrypsin Deficiency (AATD) is an uncommon and often undiagnosed genetic disorder, with estimates of 100,000 (1 in 3,000) individuals having the most severe forms (ZZ and Z null phenotypes). Another 8 million may be carriers of the Z gene (MZ phenotype). However in the context of a family member who already has been identified with the deficiency, the odds are very different for other family members.

In reviewing the Alpha Coded Testing (ACT) Study for enrollees between January 2002 and October 2004, the study enrolled 2,831 persons who requested a free and confidential, self-administered finger-stick test kit. We were surprised to see that 422 individuals (212 male and 208 female) were less than 18 years of age.

We therefore decided to assess and review the opinions of their parents through questionnaires about the risks and benefits of testing. Regardless of the parental desire to test their children, there are many controversial issues surrounding genetic testing of minors.

Genetic testing involves examining an individual’s DNA (the genetic instructions or blueprints for biological development) extracted from a blood or tissue sample. There are over 900 genetic tests available including tests for Huntington disease, Tay-Sachs disease, Duchenne muscular dystrophy, sickle cell anemia, homocystinosis, certain predisposition genes for various cancers, and Alpha-1 Antitrypsin. Although personally unique, the information attained from genetic testing impacts the entire family. The long and short-term consequences of genetically testing children and adolescents are likely different for different diseases. Risks and benefits concerning genetic testing usually fall within three categories: psychosocial, ethical, and medical.

Several academic societies and committees have made suggestions for childhood genetic testing. These recommendations vary according to type of test, however most recommend testing children when there is a medical benefit. The American Academy of Pediatrics (AAP) committee on bioethics (2001) does not suggest testing of children and adolescents for adult-onset conditions like Alpha-1. However, the AAP supports testing if (a) the minor expresses interest and gives assent, (b) the parents provide informed consent and (c) information pertaining to the risks and benefits of testing is discussed prior to testing.

The American Cancer Society reports that most smokers start in their teen years (12-17 years of age). The younger the age when starting, the more likely they are to develop nicotine addiction. The likelihood for a teenager to start smoking greatly increases if friends and/or parents smoke. Research has shown second hand smoke also has potentially harmful effects on an individual. In 2003, it was reported 1 in 4 high school students used some form of tobacco and 1 in 5 were current cigarette smokers.

The single most effective way to delay and prevent Alpha-1 lung disease is to avoid cigarette smoking. Therefore, others have asked whether Alpha-1 testing is medically, socially and ethically beneficial for children and adolescents. The decision to use genetic tests on children and adolescents at risk for Alpha-1 will continue to be controversial and ultimately decided by parental choice. We all believe that the decision should be an informed and educated one for your family.

Genetic counseling, informed consent, and confidentiality should all be addressed before, during and after the testing process.

The Registry through the ACT study has begun some targeted studies of the feelings of parents who test their children. It should not be much of a surprise that these parents who choose to test their children believe the benefits far outweigh any risks. Since we believe that an informed decision that results in a confidential test should be a standard in the American medical system, we will continue to enroll minors in the ACT study while attempting to assure that enough support is present for participants to understand the implications for their lives.

Please call the Alpha-1 Research Registry toll-free 877-886-2383 for further questions regarding genetic testing of children and adolescents.

![Figure 1: Age distribution, Minors in ACT Study](image)
Registry Family Linkage Study: Alpha-1 Family Communication is Good
by Rebecca Page, PhD
Alpha-1 Fellow
Medical University of South Carolina

Since June of 2003, the Alpha-1 Foundation Research Registry questionnaire has had a section called Family Linkage. This section requests that individuals speak with family members if they also have Alpha-1 or are carriers, and obtain their permission to be contacted by Registry personnel. If family members give enrollees their permission to be contacted, then those names and contact information are included on the Family Linkage section of the Research Registry form.

In the fall of 2004, we reviewed the Family Linkage program with study members. The objective of the study was to verify the numbers of linked enrollees and to assure that enrollees were contacting Family Linkage members. It was found that of all who were surveyed, 100% had given their permission to other family members. Figure 2 shows that about 40% of Research Registry enrollees are enrolling in Family Linkage. Furthermore, the participation of family members has driven a large part of Registry enrollment in the past two years. Since we all know that Registry numbers are an important message to the Alpha-1 community, the Family Linkage program has been important. Our hope is that future studies can use the Registry families to help unravel the mysteries of Alpha-1.

Initial Findings and Project Summary: From the inception of the database in 2002 until Sept. 1, 2004, 500 names were submitted by Registry members. These individuals were contacted by mail (499) and telephone (100) and resulted in 100 individuals willing to be linked in the database as family members.

A focused interview of 20 individuals who did not respond to the mailing showed that reasons for non-response included the following:

- not being an Alpha-1 deficient/carrier and therefore not eligible to join (3)
- no interest in participation because they did not understand what was being requested/general confusion (1)
- awaiting test results (3)
- just received the application/working on returning it (10)
- vision problems and requested large font version (1)
- it was in the mail (1)
- and never received questionnaire/please send another (1)

Conclusion: We conclude that family members were indeed speaking with other family members concerning Alpha-1 and were obtaining their permission before forwarding their names. Furthermore, voluntary participation in the linkage was indicated to be very favorable. This small study highlights the difficulties in obtaining family members for genetic studies due to time constraints, in terms of filling out Registry forms, and awaiting test results. It also demonstrates the increased recent interest in participation of family members.

This survey is important not only for reasons of confidentiality but as an indication of the positive communication in families regarding Alpha-1. As a result, plans are currently underway for a continuation of this survey to begin shortly.
Research Update

Alpha-1 Foundation Research Activities,
September 2004 – May 2005
by Syma Finn
Director of Research and Grant Programs
Alpha-1 Foundation

Alpha-1 Foundation Grant Program
Peer-Reviewed Grant Program: A total of 27 research, pilot and postdoctoral fellowship grants were submitted and reviewed in this year’s grant cycle. In addition, five meeting grant proposals and two travel grant requests were submitted for consideration of funding in the 2006 fiscal year. The Grant Review Working Group met in Miami on Saturday, February 19th and provided a scientific peer review and merit score for each of the grants. Eight of the 27 research projects and two of the meeting grants submitted received fundable scores and were considered highly relevant to the Foundation’s mission. Funding decisions will be made in May by the Administrative Review panel and announcement of newly funded projects was made at the Board meeting on May 15th.

Matching Grant Programs: The Alpha-1 Foundation continues to jointly fund research through matching grant programs with the American Lung Association, American Thoracic Society, American Liver Foundation and the National Heart, Lung & Blood Institute-National Institutes of Health. These organizational relationships have been successful at increasing basic funding and expanding the number of investigators who focus on projects that are relevant to Alpha-1. Specific awards include the ALA-A1F grant, which was recently awarded to Adrian Shifren, MD, Washington University, St. Louis. Other matching grant awards are under consideration with the NHLBI, ALF, CHEST and ATS.

Travel Grants Promote Exchange of Foundation-Funded Alpha-1 Research: Promoting the exchange of Alpha-1 research data is a primary goal of Foundation’s Travel Grants, which are awarded to provide the means to present new and exciting scientific findings of Foundation-funded projects or for the recipient to otherwise participate in Alpha-1 scientific meetings. The first Travel Grant submitted in this program was awarded to Connie Guaqueta, MD, University of Miami, Center for Liver Diseases, for a poster presentation on the role of Alpha-1 Antitrypsin in chronic liver disease. This poster was presented at the 55th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD). A second travel grant is being awarded to Sabina Janciauskiene, MD, a promising young investigator from Lund University in Sweden, to attend the American Thoracic Society annual meeting to present the results of her research on Alpha-1.

A1F Working Groups, Advisory Committees Activities
The Foundation convened a number of working group and advisory committee meetings over the past year including meetings of the Ethical, Legal and Social Issues (ELSI) Working Group, Tissue Bank Advisory Committee, Medical and Scientific Advisory Committee (MASAC), Epidemiology Working Group and Grant Review Working Group. A meeting of the Grants Advisory Committee was held on Saturday, May 14, 2005.

ELSI Working Group: The ELSI Working Group initiated actions, as requested by Miriam O’Day, Senior Director of Public Policy, to address the Alpha community concerns regarding the new UNOS proposal for distribution of lungs.

Tissue Bank Advisory Committee: The Tissue Bank Advisory Committee meeting reviewed the impediments to achieving its goal of 1,000 DNA samples from ZZ, MZ and control subjects and made specific recommendations for the coming year’s activities.

MASAC: The MASAC meeting included a discussion with representatives from Baxter Healthcare regarding observations about Aralast. Subsequent to the discussion at MASAC, Dr. Brantly traveled to Austria to meet with the scientists at Baxter. He reports that Baxter has identified the biochemical basis of the problem and has sent this information to the FDA. Dr. Brantly will provide more information in the near future of the results of the FDA review, and any actions taken regarding production of Aralast.

Epidemiology Working Group: The Working Group held its annual face-to-face meeting in February. The Working Group welcomed new members Tomas Sveger, MD from Lund University in Sweden; Fred Kueppers, MD, Temple University; David Mannino, MD, University of Kentucky, and Ray Moseley, PhD, University of Florida each of whom brought needed expertise to the group. Discussions included what prevalence figures the Foundation should use in its publications, what is an adequate test for Alpha-1, preventive measures, epidemiological topics to be included in the Foundation’s Research agenda, and the role the Working Group (WG) should play in overseeing Foundation medical and scientific activities. The Foundation also implemented the recommendations of both the EPI WG and the ELSI WG and appointed additional members to the Educational Materials WG from these other two WGs. This will ensure that input from experts in epidemiology and bioethics will be incorporated into the Foundation’s educational materials at an earlier stage in their development. The members appointed to the EMWG were David Mannino, MD (EPI WG member) and Marilyn Coors, PhD (ELSI WG member).

Grant Review Working Group: As noted above in this report, the scientific grant review was conducted on February 19th by the members of the Grant Review Working Group. Bruce Trapnell, MD, Chair and David Lomas, MD, Vice-Chair guided the committee through the difficult task of evaluating individual research project applications. The Foundation commends the efforts of Dr. Trapnell to annually refine and improve this process, and to both he and Dr. Lomas for ensuring that the review process is fair and identifies the most relevant and feasible projects for the Foundation to fund.

Bruce Trapnell, MD
Scientific Meetings and Alpha-1 Education Days

The Foundation participated or organized several scientific meetings in 2004-5:

- **European Respiratory Society (ERS) Annual Meeting** in Glasgow, Scotland. The Foundation exhibited at the ERS for the first time in four years to promote the recently published ATS/ERS recommendations on Alpha-1 testing. The Glasgow meeting also afforded the Foundation the opportunity to meet with the leadership of the Alpha-1 International Registry (AIR). Drs. Stolk and Stockley, to explore coordination on projects of mutual benefit to the Foundation and AIR.

- An **NIH State of the Science meeting on COPD** was held at the NIH in the Washington, DC area on September 29-30, 2004. The meeting was attended by the Foundation’s Scientific and Clinical Directors (Drs. Trapnell and Sandhaus) and presentations were given by Drs. Silverman and Brantly among others. The meeting incorporated state of the art presentations on Alpha-1 Antitrypsin Deficiency and COPD.

- A scientific session on Alpha-1 and other metabolic liver diseases was held at the annual **American Association for the Study of Liver Diseases (AASLD)** meeting in Boston on October 31, 2004. Drs. David Perlmutter and David Brenner chaired the session. The interest in this Alpha-1 session was so tremendous that the meeting room was completely filled, people sat in the aisles and against the back wall and over 100 people were turned away. The AASLD also highlighted the importance of Alpha-1 by tapping Dr. Perlmutter to give the Hans Popper Memorial Lecture, where he provided a thorough overview of current research in the field.

- **Critical Issue Workshop #9**: The Foundation convened the 9th in its Gordon L. Snider Critical Issue Workshops series on April 8, 2005. The workshop, **AAT Standards**, was convened to promote standardization among the international Alpha-1 community of the quality and quantity of alpha-1 antitrypsin purified from various sources. There is an urgent need for this standardization in order to accelerate the development of therapies for AAT deficient individuals. The workshop explored what characteristics define AAT, what is the optimal purity and functionality, and what specific techniques scientists should use to measure those characteristics. The workshop brought together more than three dozen international investigators from academia and industry, and key government regulators from the U.S. and Europe. The workshop, and a subsequent writing group session, was successful at achieving consensus on which methods to use, and what constitutes a “gold standard” in purity and functionality of AAT. A timeline for establishment of an international standard was established and plans were made to submit an application to the World Health Organization (WHO) for this standard by 2006.

The workshop was chaired by Mark L. Brantly, MD, University of Florida and N. Gerald McElvaney, MD, Royal College of Surgeons, Dublin. Awards were presented during the workshop to James M. Travis, MD and Friedrich Kueppers, MD for their early research of Alpha-1 as well as recognition of their ongoing work on the biochemistry of AAT. There are plans for a publication on the results of the workshop within the coming year.

**Rare Lung Disease Consortium 2nd Annual Conference**: Over 200 patients and scientists from around the world attended the Rare Lung Disease Consortium’s 2nd Annual International Conference and Investigator Meeting in Cincinnati, Ohio on April 8-10, 2005. The conference was anchored by two combined sessions, which focused on topics that bridge many rare lung diseases: inflammation, fibrosis, autoimmunity, and misfolding. Individual diseases were addressed in seven smaller scientific sessions. The diseases included were Alpha-1, LAM, PAP, children’s interstitial lung disease, connective tissue interstitial lung disease, tuberculous sclerosis and mucociliary clearance diseases.

The conference included patient advocacy group meetings including two new patient foundations, the PAP Foundation and the childLD Foundation. These two new foundations held their first meetings at the 2005 conference. The RLDC dinner on Friday night focused on the patient foundations that were represented at the conference. The presidents of the patient groups, including John W. Walsh, gave updates on their foundations and how the latest scientific findings have affected their communities. It was clear from the presentations, and the scientists’ feedback, that involving patients as active participants at scientific meetings has a tremendously positive impact on the investigators, and gives the patients and their families a feeling of greater involvement as well as providing much needed knowledge about their condition(s). The Alpha-1 Foundation also held a very successful Education Day on Saturday.

**Upcoming Scientific Meetings in 2006:**

- **Liver Research Conference**: Drs. David Perlmutter, Bruce Trapnell and William Balistreri have organized a Single Topic Conference on Alpha-1 that will be held January, 26-28, 2006 at Emory Conference Center in Atlanta, GA. Given the interest in Alpha-1 at the AASLD Annual meeting, we expect this Single Topic Conference to be a well-attended and productive meeting for the Foundation.

- **Imaging Technologies Workshop**: Drs. John Newell, Jr., National Jewish Medical & Research Center and Jan Stolk, Leiden University, are in the early stages of organizing the 10th Critical Issue Workshop on Imaging Technologies for Alpha-1 and Other Lung Diseases. This workshop will be held on Feb 10, 2006 in Washington DC and involve both US and European experts in radiology, pathology, pulmonology, biology, physiology and physics. The workshop will present on the various imaging technologies and its possibilities for non-invasive diagnosis of lung disease progression. The workshop will also include discussions on other emerging issues in the field of thoracic imaging such as imaging based efficacy testing of new drug developments and palliative treatments that could treat emphysema without surgery.
Update on Gene Therapy Trial at the University of Florida

by Terrence Flotte, M.D.
Powell Gene Therapy Center, University of Florida

Investigators at the Powell Gene Therapy Center (PGTC) at the University of Florida are conducting the first human trial of gene transfer for AAT Deficiency. The technique involves the use of a virus (which does not cause disease) called adeno-associated virus (or AAV), which can insert normal genes into cells and reprogram those cells to produce large amounts of the normal AAT protein. The AAV virus carrier is injected into muscle. The muscle cells serve as factories for continuous production of the normal AAT protein, providing a sustained release of that protein into the bloodstream. This technique has been very successful in preclinical studies in mice and non-human primates. If this technique works in humans, once the desired blood levels have been reached, we hope the protein will protect the lungs from the harmful effects of enzymes released from the white blood cells, thus replacing the normal function that Alphas are lacking.

A major investment was required to satisfy all of the regulatory requirements mandated by the Food and Drug Administration, the National Institutes of Health, and other local agencies. It was important to repeat the animal studies in different animals to be certain that there was no unwanted inflammation triggered by the virus vector and to be sure that the gene did not spread beyond the intended administration. The PGTC developed specialized facilities for the production of the patient-grade batch of the AAV-AAT vector. The production was completed and after the vector was tested for potential impurities the patient trial began.

In this first trial the AAV virus carrier, or vector, is being injected into the patients' upper arm muscle of their non-dominant hand. In giving the injections the doctor is guided using sound to detect the location of the blood vessels so that the injections are not into the vein. As this is the first time that this vector has been given, this is a Phase I safety trial commencing with a very small dose in cohort one, slowly escalating to four cohorts with increasing doses; 3 subjects in each cohort. The purpose of this trial is to test the safety of injecting the AAV-AAT vector into the muscle. The trial began a year ago and 8 subjects (presently in cohort 3) have been dosed with no reported serious adverse events. The trial will study 12 relatively healthy Alphas with the common Pi*ZZ gene mutations and without liver disease.

Future plans involve the commencement of another clinical this year using another type of the adeno-associated virus and development of vectors for Alpha deficient individuals with liver disease. Dr. Terry Flotte is the Principal Investigator (PI). The clinical team involved in this trial is composed of a clinical research group that includes Dr. Mark Brantly, Alpha-1 Professor of Medicine at UF, the Co-PI, Dr. Barry Byrne, Director of the PGTC, Dr. Terry Spencer, Dr. Carolyn Spencer, Dr. Wendy Garlington, Dawn Baker, ARNP, and Margaret Humphries, R.N. The vector production team is headed by Dr. Richard Snyder, of the UF Department of Molecular Genetics and Microbiology. The regulatory team includes Dr. Joyce Francis, Director of Quality Assurance.

These studies are being funded by a combination of sources, including the National Heart, Lung, and Blood Institute, Shands Hospital at UF, the UF College of Medicine, the Alpha-1 Foundation, the General Clinical Research Center, and Mercy Medical Airlift.

Questions concerning this study may be directed to Margaret Humphries 1-800-749-7424, ask for Pediatric Pulmonary or (352) 846-2286
The Impact of Alpha-1 on Siblings

by Joanna H. Fanos, PhD,
Dartmouth University

Alpha-1 is a young disease, barely 40 years old. There have been no studies of the impact of Alpha-1 on brothers or sisters. Approximately two years ago I advertised through the Registry to find 25 persons who had a brother or sister with Alpha-1. My aims were to:

1) learn how well Alphas understand the genetics of the disease;
2) determine if Alphas recommend Alpha-1 testing of children, and
3) assess the psychosocial impact of growing up with a brother or sister with Alpha-1.

Hour-long phone interviews yielded very interesting findings:

**Knowledge of Genetics of Alpha-1:** Seventy-six percent of individuals correctly understood that if a child had PiZZ Alpha-1, both parents have to be carriers or PiZZ-affected individuals. A majority (56%) of participants overestimated the percentage of individuals diagnosed in the US who have Alpha-1, probably based on their own experience. Eleven participants (44%) answered correctly that if both parents carry one copy of the gene (the most common scenario), each child would have a 25% chance of having severe AAT Deficiency (PiZZ). Four believed 100% of offspring would be severely affected. The 50% carrier risk for each child of carrier (PMZ)-x-carrier (PiMZ) couples was answered correctly by 15 individuals; five believed all children would be carriers.

**Attitudes Toward Testing of Children:** Eighteen of the 25 participants thought it was a good idea to test a child, three did not know, and four felt children should not be tested, primarily citing insurance concerns. Of those 18 who stated it was a good idea, 14 would test at birth.

**Change in Health-Related Behaviors:** Thirty-three percent of individuals identified as PiMZ had altered some health behaviors after learning their status. Others had already done so (e.g., stopping smoking), for related health issues (e.g., asthma), and continued to avoid smoking. Settings or other toxic factors in the environment. Of those identified as PiZZ, 60% had stopped smoking at diagnosis and had become more aggressive in avoiding other environmental toxins following diagnosis; others had never smoked or had already stopped smoking.

**Psychology of Participants:** The majority of participants, both PiZZ’s and PiMZ’s, had adapted well to their respective situations. However, in some families, communication about the illness had been poor and family secrets prevailed. Some parents never mourned their loss, creating a climate of sadness. A few persons recalled traumatic experiences related to siblings with severe liver disease and swollen bellies or bleeding. Some parents had difficulty attaching to their other children because they remained grieving and depressed.

For those who encountered Alpha-1 in adulthood, major issues related to the need for earlier identification of carriers, particularly in affected families. Some sibs with children had inadvertently learned of their status through the identification of their children. Two of the most distressed individuals had been identified as carriers in the middle of donor testing for liver transplant for an affected relative. Therefore, I offer the following recommendations:

1) Families who have a child with AAT Deficiency are at particular risk for difficulties. Young children are at risk for traumatic responses and genetic misunderstanding; parents need help mourning the loss of their child so family secrets will not prevail and emotional involvement with remaining children can be assured.
2) Teams evaluating donors for liver transplantation, particularly with a family history, should be aggressive in ruling out AAT Deficiency prior to invasive testing.
3) Testing should be recommended for adult brothers and sisters of affected individuals so they would have the opportunity to begin health modifications. Individuals should be helped to weigh potential risks and benefits.
4) Awareness of the potential for liver disease in AAT Deficiency should be increased and risk factors for liver disease medically defined.

This research has recently been published: Fanos JH, Strange C: “The Lion, the Witch and the Wardrobe”: Impact on Sibs of Individuals with AAT Deficiency. American Journal of Medical Genetics 2004 Oct 15; 130A(3):251-257.

It has been an honor working with Alphas. Thank you for allowing me to use your Registry to understand the experience of families living with this condition.
Survey About Asthma and Alpha-1

by Edward Eden, M.D.,
Chief of Pulmonary and Critical Care Medicine at St Luke's Roosevelt Hospital Center at Columbia University in New York City

Asthma is a common condition in Alpha-1 says Dr. Ed Eden, Chief of Pulmonary and Critical Care Medicine at St Luke's Roosevelt Hospital Center at Columbia University in New York City. This statement is based on recently completed work describing the findings in 757 participants of the Alpha-1 Foundation Registry questionnaire study about asthma. The work was performed in collaboration with Dr. Charlie Strange, Director of the Registry and his team. Unlike COPD, asthma is a condition of airway narrowing that can be reversed by medications called bronchodilators. It is often associated with sensitivity to airborne allergens that can be inherited as a condition called atopy. The study finds that asthma is common both when persons with Alpha-1 have developed COPD and also before the onset of emphysema. It is also commonly present in carriers as well as those with the severe deficiency (PiZZ) and others with more unusual forms of Alpha-1 Antitrypsin Deficiency.

There are several important issues that can affect the lung health of an Alpha who also has asthma. The presence of asthma can lead to a greater decline in lung function than that seen in studies with atopy. Asthma can cause significant reduction in quality of life for Alphas by reducing the sensitivity to these allergens. Avoidance of triggers of asthma such as dust, fumes, allergens and pet dander, which were reported as triggers in the study, can cut down on symptoms.

Asthma may be the first presenting symptom in a young Alpha who has not yet developed COPD. Recognition of this may lead physicians to consider Alpha-1 as a diagnosis. However, because asthma is such a common condition, the only practical way to do this is screen young asthmatics for Alpha-1 Antitrypsin Deficiency. Unfortunately, testing in an unselected asthma population has not found many Alpha-1 cases.

The recent American Thoracic Society/European Respiratory Society statement recommends testing for Alpha-1 in some asthmatics whose pulmonary function does not reverse completely after therapy.

Another issue that is important in the early identification of Alphas is the question of proper diagnosis. This paper addresses some of these issues such as bias. Just as racial bias exists so physicians are biased in choosing diagnosis for their patients. Younger patients may be diagnosed with asthma even though they have early COPD. The findings indicate that the diagnosis of asthma may be delayed from 4-7 years after the onset of wheezing symptoms and that some subjects who wheeze are never given a diagnosis. This may be due to patients not reporting their symptom to their doctors or the doctors not picking up on the condition even when mentioned by the patient. It is true that not many younger individuals go to the doctor on a regular basis.

What about treatment with augmentation therapy that is expensive and has relatively small effects on the decline in lung function? Does treatment have any impact on asthma symptoms? The first finding in the study is that subjects on augmentation have a lot more asthma symptoms than those not on the therapy. This is probably because those who receive augmentation tend to have more severe lung disease so asthma symptoms are more common. The second important finding is that augmentation therapy was reported by about one-third of participants with severe deficiency to improve asthma. Raising alpha-1 levels in the airways may reduce locally produced chemicals that promote inflammation, airway narrowing and asthma.

Finally, the authors of this important study would like to thank all those who participated. This was really an Alpha-1 community effort that would not have been possible without your participation in the Registry. Thank you.
Our Alpha-1 Album

Over the last 10 years the Alpha community has been involved in a number of different activities and events, including scientific meetings, advocacy training, education days and sporting events. The commitment of our medical and scientific partners plays a huge role in the lives of our Alphas.
News Flashes

Development and Communications
Emily Marquez-Dulin
Senior Director of Communications
Alpha-1 Foundation

National Targeted Detection Program takes on a Florida test
Aiming to test thousands of symptomatic patients across the U.S., the Foundation has embarked on a Florida pilot test of all the strategies and tactics outlined for the National Targeted Detection Program. Testing the strategies and tactics outlined for the 10-market national rollout in one market provides a platform to measure and evaluate the effectiveness of the program.

The organization decided to concentrate its programming in Florida as the state with the nation’s fourth largest overall population and the fourth highest number of patients with chronic obstructive pulmonary disease (COPD). The Foundation is headquartered in Florida and resources are easily accessible. It is also in the process of celebrating its tenth anniversary and considerable media coverage for Alpha-1 is expected. Most importantly, strong benchmarks exist in Florida by which to judge the effectiveness of the techniques being applied.

The goal of the National Targeted Detection Program is simple, but enormously ambitious. The plan calls for the diagnosis of Alphas among patients already showing symptoms, so that they can receive proper treatment, manage their disease, and live longer. Raising awareness of Alpha-1 among the targeted population will also spur research toward a cure. Recently, the American Thoracic Society and the European Respiratory Society recommended Alpha-1 testing for everyone with emphysema, COPD, asthma with airflow obstruction that is incompletely reversible after aggressive treatment with bronchodilators, and unexplained liver disease. COPD patients alone number more than 10 million in the U.S.

In Florida, the Foundation is using a “push-pull” marketing approach, aiming both at physicians who treat COPD patients (pull) and at patients directly (push). Pull tactics included ad placement in the Florida Medical Association (FMA) Quarterly, a statewide medical journal distributed to more than 16,000 physicians, and e-mail alerts to nearly 60,000 pulmonologists, hepatologists, internists, primary care physicians and respiratory therapists. The program has also furnished hospitals and other institutions with media kits for their newsletters, sent letters to 825 Durable Medical Equipment and oxygen companies, and hosted a COPD/Alpha-1 Education Day in Miami.

Patient-focused efforts included advertising in regional editions of the American Association of Retired Persons (AARP) magazine which is circulated to more than 1.5 million people, distributed over 96,000 email alerts to individuals with pulmonary and liver disorders who were interested in added information, media coverage in local and regional outlets, public service announcements, and speakers at community and civic groups.

Preliminary results from the email distribution are promising in all categories (provider and direct-to-patient) with an increase in website visits (www.shortofbreathgettested.org) of 86.5% in a 30-day period following distribution. Based on Florida’s results, the Foundation will refine and adapt those tactics in nine other markets—New York, New Jersey, Pennsylvania, Ohio, North Carolina, Michigan, Georgia, California, and Texas. The rollout will move east to west, using states with Alpha-1 clinical resource centers as stepping-stones, and conclude with the states largest in geographic area. We hope that all of you will promote this program when it comes to your area of the country.

New outreach campaign recently launched to increase awareness and raise funds for Alpha-1
Building Friends for a Cure is a community friend-building campaign that supports Alphas as they network with neighbors, friends, and local and regional media to build awareness, raise funds and get us closer to a cure. The campaign is designed to extend the geographic reach of the Alpha-1 Foundation, and foster stronger links between the organization, Alphas and the community at-large.

The need to increase testing among at-risk populations is at an all-time high, and the only way to do this is through coordinated efforts across the country. The more people who learn about Alpha-1 Antitrypsin Deficiency, the higher the likelihood of increased testing. Everyone who hears about Alpha-1 becomes an immediate ambassador for the cause and will pass on the message to others.

Every Alpha has a compelling story to tell. And every Alpha’s story holds significance for the whole community. An Alpha’s story can lead directly to earlier detection, better treatment, and longer lives for undiagnosed Alphas still searching for answers.

Local TV, newspaper, and magazine journalists rely on the public to generate leads for their stories, particularly for human-interest features that alert their audience to little-known health issues. Each
Alpha can provide such a story. No one can speak about the challenges of living with a little-known disorder better than an Alpha.

Volunteers and friends play a huge role in raising revenue to support the mission and programs of the Alpha-1 Foundation. Funds can be raised in many different ways including hosting a special event, leading a letter-writing blitz, and making personal introductions to potential donors. Alphas interested in participating in the Building Friends for a Cure campaign can choose what type of commitment they want to make and how they would like to execute such commitment.

As John W. Walsh, President and CEO, of the Alpha-1 Foundation eloquently says, “Just imagine the cumulative fund-raising power of each Alpha networking with just a handful of his or her friends and acquaintances. One Alpha asking 20 friends for a $50 contribution would raise $1,000.” Then he excitedly carries on, “Multiply that by 1,000 Alphas, and the total reaches $1 million—all of which directly supports critical Alpha-1 research.”

The Alpha-1 Foundation can help every step of the way. It has assembled a complete guide, offering detailed information and ideas for fundraisers, recruiting a committee to help, outlining a budget, and using resources available from the Foundation. It also offers how-to information on contacting and working with the media. For a free copy of Building Friends for a Cure, contact the Foundation’s Development Officer Angela McBride (888.825.7421, ext 233 or amcbride@alphaone.org).

Advocacy and Public Policy
by Miriam O’Day
Senior Director of Public Policy
Alpha-1 Foundation

Federally Funded Embryonic Stem Cell Research – What’s New?
Almost four years have passed since President Bush addressed the nation and articulated the current federal policy for funding of embryonic research. Since then, we have learned much more about the potential of research on human stem cells to open vistas of scientific research for future therapies and cures. We have also learned that the limitations placed by the existing federal policy only allows support for 22 stem cell lines, many of which are owned internationally instead of the 60 lines the administration believed were available in August 2001.

While human clinical trials are many years away, we now know that the 22 lines are intermingled with mouse cells and bovine serum which makes them ineligible for clinical treatment due to concerns about xenotransplantation. Because of these restrictions, scientists and top-level government officials have joined patient advocates in voicing their dissatisfaction with the administration’s current restrictions.

New hope for federally funded embryonic stem cell research has arisen in the form of legislation introduced by Congressman Mike Castle (R-DE) and Congresswoman Diana DeGette (D-CO).

The Stem Cell Research Enhancement Act, HR 810 has bipartisan support and follows the ethical guidelines currently in place. The Castle-DeGette legislation allows broader federal funding, while ensuring that federal funding will not be used to derive stem cells or destroy embryos. The Stem Cell Research Enhancement Act also directs the National Institutes of Health to develop appropriate ethical guidelines for future derivation of human stem cell lines. Mr. Castle has negotiated with the republican leadership to bring his (or similar legislation) to the House floor for a straight up or down vote, which may take place prior to the July 4th recess.

Embryonic Stem Cells

The Alpha-1 Foundation strongly supports HR 810, because there is nothing that currently repairs lung tissue damage and reparative medicine and therapies offer great hope for the future. The Foundation is working closely with our membership organization, the Coalition for the Advancement of Medical Research (CAMR), to educate Congressional members who are undecided or opposed. These congressional meetings raise awareness about Alpha-1 and the need to expand the federal funding. CAMR is a non-partisan not-for-profit, comprised of nationally-recognized patient organizations, universities, scientific societies, foundations, and individuals with life-threatening illnesses and disorders, advocating for the advancement of breakthrough research and technologies in regenerative medicine - including stem cell research and somatic cell nuclear transfer - in order to cure disease and alleviate suffering. For more information on CAMR, visit the website: www.camradvocacy.org

On March 25, 2005, CAMR released new polling data that shows a strong majority of Americans solidly support embryonic stem cell and therapeutic cloning research. A nationwide survey of more than 1,000 adults conducted from March 18-21, 2005 found that the more respondents learned about the research; the more they supported its use to help treat some of life’s most debilitating diseases and conditions.
Genetic Non-discrimination

The Senate once again passed positive protective legislation to prohibit genetic discrimination. By a vote of 98 in favor and non opposed S. 306, the Genetic Information Nondiscrimination Act of 2005, will now wait until the U.S. House of Representatives takes similar action and sends a bill to the President. The Foundation has joined the Alpha-1 Association in issuing an Action Alert to the Alpha-1 Community so that individuals can once again weigh in with their members. We are also working closely with the Coalition for Genetic Fairness of which we are members in good standing. As you are aware similar legislation has languished on Capitol Hill for many years and seen many opponents such as the US Chamber of Commerce and the insurance lobby.

So what's new now after nearly a decade of waiting? Sponsorship of the House bill Genetic Information Nondiscrimination Act of 2005 H.R. 1227 has changed hands to republican Judy Biggert from Illinois. Past sponsor Congresswoman Louise Slaughter (D-NY) was a staunch advocate for genetic nondiscrimination, however, majority party sponsorship is helping H.R. 1227 gain momentum and sign-on co-sponsors.

"Alphas need access to specialized healthcare without fear of retribution such as the loss of health insurance."

Alphas need access to specialized healthcare without fear of retribution such as the loss of health insurance. In the absence of federal legislation, states have implemented a patchwork of laws that shield individuals from employment and insurance discrimination. We need national policy to ensure that all Americans have the same protections. The Alpha-1 Foundation's Ethical Legal and Social Issues (ELSI) Working Group endorsed the recommendations of the American Thoracic Society/European Respiratory Society Standards Document on Diagnosis and Management of Alpha-1 Antitrypsin Deficiency. These recommendations are being implemented by the Foundation's National Targeted Detection Program and include testing symptomatic individuals or siblings of those who are diagnosed with Alpha-1. The absence of protective legislation has caused the ELSI to recommend against population screening and genetic testing in the neonatal population. Early diagnosis in Alpha-1 can significantly impact disease outcomes by allowing individuals to exercise preventative health measures, seek appropriate therapies, and engage in essential life planning. Unfortunately, gaining this information may lead to discrimination against individuals who have no control over their inherited condition. Call or write to your member of Congress today, ask them to sign on as a co-sponsor of H.R. 1227.
Q. I have heard that Alpha-1 Antitrypsin Deficiency (AATD) can cause liver disease in adults as well as in children. Is this something I should be worried about and how do I find out if my liver is affected?

A. Though the initial descriptions of the illness caused by AATD were of lung disease, by 1969 it was recognized that severe Alpha-1 Antitrypsin Deficiency could also cause hepatitis (inflammation of the liver) with cirrhosis (liver scarring) in children. Most who are familiar with Alpha-1 are aware that AATD is one of the more common culprits for liver disease that causes transplantation in children. Sometimes the liver disease that begins in childhood can continue into adult life but overall the risk during childhood for severe liver disease in AATD is well below 1%.

Less commonly appreciated by the Alpha-1 Community, including many of its physicians, is that AATD can also cause liver disease in adults who never had apparent liver disease during childhood. One of the myths about AATD is that people either get lung disease or liver disease but never both. Recent studies of those Alphas who have survived into their elder years have clearly found that a significant percentage of them succumb to liver disease, including cirrhosis and liver cancer later in life. Generally these Alphas are those who never smoked - those who did smoke tend to develop lung disease and die at a younger age. It is not to say Alphas who manage to avoid lung disease are inevitably going to die of liver disease – none of these risks are 100%. But knowing these risks helps doctors manage the health problems specific to Alphas. Ultimately, understanding these risks should also help researchers develop new therapies to prevent the liver disease as well as the lung disease.

The risk for liver disease in Alpha-1 Antitrypsin Deficiency appears to be most significant in those with severe deficiency – specifically, in those with the PiZZ phenotype. Other forms of AATD have a much lower risk. Alcohol consumption and viral hepatitis seem to be important as additional risk factors for those with the PiMZ heterozygous state. Alphas (like everyone else) should moderate their alcohol consumption. If evidence does surface of severe liver disease, alcohol should be avoided entirely. Vaccination against Hepatitis A and B is not known to prevent liver disease in AATD though the Hepatitis B vaccine is still recommended for those who are going to receive augmentation therapy (Prolastin, Aralast, Zemaira) since these are all blood products.

Liver disease can develop very slowly – by the time it becomes apparent the disease can be advanced. Simple liver blood tests and a thorough physical exam to look for evidence of liver disease should be conducted on a yearly basis in Alphas. More exhaustive tests like ultrasound exams or CT scans aren’t recommended unless other evidence of liver disease surfaces.

Liver disease is not just a problem in children with AATD. Adult Alphas and their doctors need to keep their eyes open for possible liver disease later in life. As we become more experienced, anticipating, recognizing and managing these problems should improve the healthcare for those with AATD.
Education Days, Events and Meetings

May 1 – October 30, 2005

May 20-25 American Thoracic Society Annual Meeting
June 10-12 Alpha-1 Association 13th Annual Education Conference
June 25 Michigan Alpha-1 Education Day
August Oregon Health & Science University & Oregon CRC Alpha-1 Education Day
August 06 National Jewish Medical and Research Center / Denver Health & Hospitals COPD & Alpha-1 Education Day (A1F Clinical Resource Center)
August 27 Omaha Alpha-1 Education Day
September University of Minnesota COPD & Alpha-1 Education Day
September 24 Las Vegas Alpha-1 Education Day
October 01 Temple University COPD & Alpha-1 Education Day
October 08 5th Annual Jean Wall Bennett Cleveland Clinic Alpha-1 Education Day
October 22 Michigan COPD & Alpha-1 Education Day (NIH-NHLBI Clinical Resource Network)

Commitments and dates are subject to change as of 5/5/5

Alpha-1 Foundation

The Alpha-1 Foundation is a not-for-profit organization dedicated to providing the leadership and resources that will result in increased research, improved health, worldwide detection, and a cure for Alpha-1 Antitrypsin Deficiency. The Foundation provides the infrastructure to promote research and the development of new therapies for improving the quality of life of those diagnosed with Alpha-1. The Foundation is committed to close collaborations with medical experts, government agencies, international regulatory authorities, the pharmaceutical industry and other organizations to jointly resolve critical issues in the field of Alpha-1 research and treatment. A Grant Award Program supports a wide range of meritorious research in Alpha-1.

You may contact the Alpha-1 Foundation Research Registry staff by email, at registry@alphaone.org for additional assistance in locating resources related to AAT Deficiency research, to obtain information about current research activities, to participate in the Research Network or Registry, or to receive Foundation publications.

AlphaNet

AlphaNet, Inc. is a unique disease management organization. Through its medical and operations staff, AlphaNet provides a wide range of integrated support services to individuals with Alpha-1 Antitrypsin Deficiency (Alpha-1) who require augmentation therapy, oversees and sponsors clinical trials involving Alpha-1 therapies, and makes available a comprehensive disease management and prevention program to improve the quality of life of those affected by Alpha-1. AlphaNet currently employs 25 Alphas as care coordinators to serve over 2,500 other Alphas. Since its inception in 1995 as a charitable not-for-profit corporation, AlphaNet has contributed over $14 million to support Alpha-1 research and fund Alpha-1 community programs.

Alpha-1 Association

The Alpha-1 Association is a member-based nonprofit organization founded in 1991 to identify those affected by Alpha-1 Antitrypsin Deficiency (Alpha-1) and to improve the quality of their lives through support, education and advocacy. The Association has over 50 volunteer-led support groups around the US which are supported through annual grass roots grants. The Education program includes an annual National Conference and co-sponsorship of regional Alpha-1 Education Days with the Alpha-1 Foundation. The Advocacy Program focuses on access to care; maintaining and extending Medicare benefits; genetic non-discrimination; increasing public health funding; traveling with supplemental oxygen; organ allocation for lung transplantation and includes working with the Congressional COPD Caucus to further our goals.